Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (currently amended) A fibronectin type III (Fn3) polypeptide monobody derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3, the polypeptide monobody comprising:

at least two adjacent Fn3 β-strand domain sequences selected from the group of A (residues 9–14 of SEQ ID NO: 2 and SEQ ID NO: 3), B (residues 17–21 of SEQ ID NO: 2 and SEQ ID NO: 3), C (residues 31–38 of SEQ ID NO: 2 and SEQ ID NO: 3), D (residues 46–50 of SEQ ID NO: 2 and SEQ ID NO: 3), E (residues 55–59 of SEQ ID NO: 2 and SEQ ID NO: 3), F (residues 67–75 of SEQ ID NO: 2 and SEQ ID NO: 3), and G (residues 88–94 of SEQ ID NO: 2 and SEQ ID NO: 3), ~~A–G~~ with an associated ~~a~~ loop region sequence linked between each pair of adjacent β-strand domain sequences, each of the loop region sequences ~~sequence~~ being selected from the group of loops AB (residues 15–16 of SEQ ID NO: 2 and SEQ ID NO: 3), BC (residues 22–30 of SEQ ID NO: 2 and SEQ ID NO: 3), CD (residues 39–45 of SEQ ID NO: 2 and SEQ ID NO: 3), DE (residues 51–54 of SEQ ID NO: 2 and SEQ ID NO: 3), EF (residues 60–66 of SEQ ID NO: 2 and SEQ ID NO: 3), and FG (residues 76–87 of SEQ ID NO: 2 and SEQ ID NO: 3)~~, and combinations thereof~~; and

optionally, an N-terminal tail of at least about 2 to about 33 amino acids, a C-terminal tail of at least about 2 to about 25 amino acids, or both;

wherein at least one loop region sequence comprises a modified ~~an~~ amino acid sequence which varies from a corresponding loop region present in SEQ ID NO:2 or SEQ ID NO:3 by deletion of up to all but one amino acid residue, insertion of two to about 25 amino acid residues, or replacement of ~~at least~~ two to all amino acid residues ~~acids from a corresponding loop region of SEQ ID NO:2 or SEQ ID NO:3~~, and

wherein the polypeptide monobody exhibits estrogen ~~nuclear~~ receptor binding activity via interaction of the at least one loop region sequence with the estrogen receptor.

2–5. (canceled)

6. (currently amended) The polypeptide monobody according to claim 1 ~~5~~, wherein the polypeptide monobody exhibits estrogen receptor binding activity in the presence of an estrogen receptor agonist or an estrogen receptor antagonist.

7. (original) The polypeptide monobody according to claim 6, wherein the estrogen receptor agonist is estradiol, estriol, diethylstilbestrol, or genistein.

8. (original) The polypeptide monobody according to claim 6, wherein the estrogen receptor antagonist is hydroxy tamoxifen, ICI182780, or raloxifene.

9. (currently amended) The polypeptide monobody according to claim 1, wherein said at least two Fn3 β-strand domain sequences comprises each of β-strand domain sequences A through G of SEQ ID NO: 2 or SEQ ID NO: 3, wherein the loop region sequences comprise ~~the combination of~~ the AB loop, BC loop, CD loop, DE loop, EF loop, and FG loop.

10. (currently amended) The polypeptide monobody according to claim 9, wherein the ~~at least one~~ loop region sequence that comprises the modified amino acid sequence is selected from the group consisting of the AB loop region sequence, the BC loop region sequence, the DE loop region sequence, and the FG loop region sequence~~, and combinations thereof~~.

11. (currently amended) The polypeptide monobody according to claim 9, wherein the ~~at least one loop region sequence is a combination of the~~ BC loop region sequence and the FG loop region sequence both comprise one of said modified amino acid sequences.

12. (cancelled)

13. (original) A fusion protein comprising:
a first portion comprising a polypeptide monobody according to claim 1 and
a second portion fused to the first portion.

14. (original) The fusion protein according to claim 13, wherein the second portion comprises a label.

15. (original) The fusion protein according to claim 14, wherein the label is an alkaline phosphatase tag or a $His_{(6)}$ tag.

16. (original) The fusion protein according to claim 13, wherein the second portion comprises a transcriptional activation domain.

17–144. (cancelled)

145. (withdrawn—currently amended) A method of validating estrogen ~~nuclear~~ receptor protein activity comprising:

exposing an estrogen ~~a nuclear~~ receptor protein to a polypeptide monobody according to claim 1 which binds to the estrogen ~~nuclear~~ receptor protein and

determining whether binding of the estrogen ~~nuclear~~ receptor protein by the polypeptide monobody modifies estrogen ~~nuclear~~ receptor protein activity.

146. (withdrawn) The method according to claim 145, wherein said exposing is carried out *in vivo*.

147. (withdrawn) The method according to claim 146, wherein said exposing is carried out in a yeast cell, bacterial cell, or mammalian cell.

148. (withdrawn—currently amended) The method according to claim 145, wherein said determining comprises:

detecting mRNA or protein expression levels prior to said exposing and after said exposing and

comparing the detected mRNA or protein expression levels to identify proteins that are downstream of the pathway of the estrogen ~~nuclear~~ receptor protein, wherein modified expression levels indicated modified estrogen ~~nuclear~~ receptor protein activity.

149. (withdrawn—currently amended) The method according to claim 145, wherein the estrogen ~~nuclear~~ receptor protein is required for cell growth or survival, said determining comprising:

measuring cell growth or survival after said exposing, wherein reduced cell growth or survival indicates inhibition of estrogen ~~nuclear~~ receptor protein activity.

150. (withdrawn—currently amended) The method according to claim 145, wherein the estrogen ~~nuclear~~ receptor protein is a pathogen protein involved in host-pathogen interaction, said exposing comprising:

exposing a host cell comprising the polypeptide monobody to the pathogen.

151. (withdrawn) The method according to claim 150, wherein said determining comprises:

determining the extent of pathogen-induced disease progression in the host cell.

152. (withdrawn) The method according to claim 150, wherein the pathogen is a bacteria.

153. (withdrawn—currently amended) A method of measuring polypeptide monobody binding affinity for an estrogen ~~a nuclear~~ receptor protein, said method comprising:

exposing an estrogen ~~a nuclear~~ receptor protein to (i) an interaction partner that binds the estrogen ~~nuclear~~ receptor protein, and (ii) a polypeptide monobody according to claim 1 that binds the estrogen ~~nuclear~~ receptor protein; and

measuring the degree to which the polypeptide monobody competes with the interaction partner.

154. (withdrawn) The method according to claim 153, wherein said exposing is carried out *in vitro*.

155. (withdrawn—currently amended) The method according to claim 154, wherein the estrogen ~~nuclear~~ receptor protein is bound to a substrate.

156. (withdrawn) The method according to claim 154, wherein the polypeptide monobody comprises a label.

157. (withdrawn) The method according to claim 156, wherein the label is an alkaline phosphatase tag or a $His_{(6)}$ tag.

158. (withdrawn) The method according to claim 153, wherein said exposing is carried out *in vivo*.

159. (withdrawn—currently amended) A method of modulating estrogen ~~nuclear~~ receptor protein activity comprising:

exposing an estrogen ~~a nuclear~~ receptor protein to a polypeptide monobody according to claim 1 that binds the estrogen ~~nuclear~~ receptor protein under conditions effective to modify estrogen ~~nuclear~~ receptor protein activity.

160. (withdrawn) The method according to claim 159, wherein said exposing is carried out *in vivo*.

161. (withdrawn) The method according to claim 160, wherein said exposing is carried out in a yeast cell, bacterial cell, or mammalian cell.

162–165. (canceled)

166. (withdrawn–currently amended) A method of detecting conformation of an estrogen ~~a nuclear~~ receptor protein, said method comprising:

exposing an estrogen ~~a nuclear~~ receptor protein to a polypeptide monobody according to claim 1 that interacts with the estrogen ~~nuclear~~ receptor protein when the estrogen ~~nuclear~~ receptor protein is in a specific conformation, under conditions effective for the polypeptide monobody to interact with the estrogen ~~nuclear~~ receptor protein, and

determining whether the polypeptide monobody interacts with the estrogen ~~nuclear~~ receptor protein, wherein interaction between the polypeptide monobody and the estrogen ~~nuclear~~ receptor protein indicates that the estrogen ~~nuclear~~ receptor protein is in the specific conformation.

167. (withdrawn) The method according to claim 166, wherein said exposing is carried out *in vitro*.

168. (withdrawn–currently amended) The method according to claim 167, wherein the estrogen ~~nuclear~~ receptor protein is bound to a substrate.

169. (withdrawn) The method according to claim 167, wherein the polypeptide monobody comprises a label.

170. (withdrawn) The method according to claim 169, wherein the label is an alkaline phosphatase tag or a $His_{(6)}$ tag.

171. (withdrawn) The method according to claim 166, wherein said exposing is carried out *in vivo*.

172. (withdrawn) The method according to claim 171, wherein said exposing is carried out in a yeast cell, bacterial cell, or mammalian cell.

173–176. (canceled)

177. (withdrawn–currently amended) A method of detecting a change in conformation of an estrogen ~~a nuclear~~ receptor protein, said method comprising:

(i) detecting conformation of an estrogen ~~a nuclear~~ receptor protein according to the method of claim 166; and

(ii) repeating said detecting after a time delay to determine whether the estrogen ~~nuclear~~ receptor protein binds to a different polypeptide monobody or to the same polypeptide monobody but with a different degree of interaction;

wherein binding to a different polypeptide monobody or a change in degree of interaction with the same polypeptide monobody indicates change in conformation of the estrogen ~~nuclear~~ receptor protein.

178. (withdrawn–currently amended) The method according to claim 177, further comprising exposing the estrogen ~~nuclear~~ receptor protein to a ligand prior to step (ii).

179. (withdrawn) The method according to claim 178, wherein said exposing is carried out *in vitro*.

180. (withdrawn) The polypeptide monobody according to claim 1, wherein the FG loop region sequence comprises the amino acid sequence selected from the group of SEQ ID NO: 20 and SEQ ID NO: 32.

181. (currently amended) The polypeptide monobody according to claim 1, wherein the BC loop region sequence comprises the amino acid sequence ~~selected from the group~~ of ~~SEQ ID NO: 22,~~ SEQ ID NO: 23~~, and SEQ ID NO: 24~~.

182. (currently amended) The polypeptide monobody according to claim 1, wherein the FG loop region sequence comprises the amino acid sequence ~~selected from the group~~ of ~~SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO:~~

~~65, SEQ ID NO: 66,~~ SEQ ID NO: 67~~, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, and SEQ ID NO: 73~~.

183. (currently amended) The polypeptide monobody according to claim 1, wherein the AB loop region sequence comprises the amino acid sequence ~~selected from the group~~ of SEQ ID NO: 34 ~~and SEQ ID NO: 35~~.

184. (cancelled)

185. (currently amended) A fibronectin type III (Fn3) polypeptide monobody comprising the formula β_A–L_{AB}–β_B–L_{BC}–β_C–L_{CD}–β_D–L_{DE}–β_E–L_{EF}–β_F–L_{FG}–β_G, wherein:

β_A, β_B, β_C, β_D, β_E, β_F, and β_G are, respectively, β-strand domain sequences A through G of a tenth Fn3 domain of fibronectin;~~,~~ and

L_{AB}, L_{BC}, L_{CD}, L_{DE}, L_{EF}, and L_{FG} are, respectively, loop region sequences AB, BC, CD, DE, EF, and FG, wherein at least one loop region sequence selected from the group of AB, BC, and FG~~, and combinations thereof,~~ varies from a corresponding loop region present in the tenth Fn3 domain of fibronectin by deletion of up to all but one amino acid residue, insertion of two to about 25 amino acid residues, or replacement of ~~at least~~ two to all amino acid residues; ~~acids from a corresponding loop region in the tenth Fn3 domain of fibronectin,~~ and

wherein the polypeptide monobody exhibits estrogen ~~nuclear~~ receptor binding activity via interaction of the at least one loop region sequence with the estrogen receptor.

186. (new—withdrawn) The polypeptide monobody according to claim 1, wherein the BC loop region sequence comprises the amino acid sequence selected from the group of SEQ ID NO: 22 and SEQ ID NO: 24.

187. (new—withdrawn) The polypeptide monobody according to claim 1, wherein the FG loop region sequence comprises the amino acid sequence selected from the group of SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ

ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, and SEQ ID NO: 73.

188. (new—withdrawn) The polypeptide monobody according to claim 1, wherein the AB loop region sequence comprises the amino acid sequence of SEQ ID NO: 35.

189. (new) A fibronectin type III (Fn3) polypeptide monobody derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3, the polypeptide monobody comprising:

at least two adjacent Fn3 β-strand domain sequences selected from the group of A (residues 9–14 of SEQ ID NO: 2 and SEQ ID NO: 3), B (residues 17–21 of SEQ ID NO: 2 and SEQ ID NO: 3), C (residues 31–38 of SEQ ID NO: 2 and SEQ ID NO: 3), D (residues 46–50 of SEQ ID NO: 2 and SEQ ID NO: 3), E (residues 55–59 of SEQ ID NO: 2 and SEQ ID NO: 3), F (residues 67–75 of SEQ ID NO: 2 and SEQ ID NO: 3), and G (residues 88–94 of SEQ ID NO: 2 and SEQ ID NO: 3), with an associated loop region sequence linked between each pair of adjacent β-strand domain sequences, each of the loop region sequences being selected from the group of loops AB, BC, CD, DE, EF, and FG; and

optionally, an N-terminal tail of at least about 2 to about 33 amino acids, a C-terminal tail of at least about 2 to about 25 amino acids, or both;

wherein at least one loop region sequence is modified from the corresponding loop region of SEQ ID NO: 2 or SEQ ID NO:3, the at least one loop region sequence being selected from the group of (i) the BC loop region sequence comprising the amino acid sequence of SEQ ID NO: 23, (ii) the FG loop region sequence comprising the amino acid sequence of SEQ ID NO: 67, and (iii) the AB loop region sequence comprising the amino acid sequence of SEQ ID NO: 34; and

wherein the polypeptide monobody exhibits estrogen receptor binding activity via interaction of the at least one loop region sequence with the estrogen receptor.